A prospective cohort study on Allium vegetable consumption, garlic supplement use, and the risk of lung carcinoma in The Netherlands

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A Prospective Cohort Study on *Allium* Vegetable Consumption, Garlic Supplement Use, and the Risk of Lung Carcinoma in the Netherlands[1]

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ABSTRACT

The association between the consumption of onions and leeks (vegetables belonging to the *Allium* genus), garlic supplements, and the risk of lung carcinoma was investigated in a large-scale prospective cohort study on diet and cancer in the Netherlands. The Netherlands Cohort Study was started in 1986 among 120,852 men and women, ages 55–69 years, by collecting information on usual diet and important life-style characteristics. After 3.3 years of follow-up, 550 incident lung carcinoma cases were observed. Information on *Allium* vegetable consumption was available for 484 lung carcinoma cases and 3123 members of a randomly sampled subcohort. In stratified analysis, a lower lung carcinoma risk was observed in the highest onion intake category [rate ratio (RR) = 0.65; 95% confidence interval, 0.45–0.95] compared to the lowest consumption category. After including other, dietary and nondietary, determinants of lung carcinoma in the multivariable models and using pack years for past and current smoking, instead of using smoking status categorized as never, ex-, and current smoking, the rate ratio in the highest intake category increased to 0.80 and was no longer significantly different from unity (95% confidence interval, 0.52–1.24). Leek consumption was not associated with risk for lung carcinoma (RR = 1.08; 95% confidence interval 0.80–1.45 in the highest intake category, compared to the lowest). No statistically significant trends in the rate ratios associated with increasing consumption of these vegetables were detected for lung carcinoma or the four histological subtypes. A higher lung carcinoma risk was observed for those subjects who used exclusively garlic supplements (RR = 1.78; 95% confidence interval, 1.08–2.92), compared to those not taking dietary supplements. A lower lung carcinoma risk was seen for those using garlic supplements together with any other supplement (RR = 0.93; 95% confidence interval 0.46–1.86) compared to those using any other supplement. In conclusion, we found no evidence of a relation between the consumption of onions or leeks and the risk of lung carcinoma or any of the histological subtypes. Garlic supplement use seems not associated with a lower risk of lung carcinoma.

INTRODUCTION

The possible inverse association between *Allium* vegetable consumption and cancer risk is a subject of growing interest. In a recent review on the relation between vegetable and fruit consumption and cancer, Steinmetz and Potter (1) identified 12 case-control studies in which an association between *Allium* vegetable consumption and specific sites of cancer had been investigated. In eight of these studies a negative association with cancer was reported; one study showed no association and three a positive association.

It has been shown in experimental studies that fresh garlic (*Allium sativum* L.), garlic oil, and specific compounds of garlic possess *in vitro* antimutagenic properties and might even exhibit *in vivo* anti-initiating or antipromoting activity against a variety of carcinogens. The results of these studies, however, are not conclusive (2). Other plants belonging to the genus *Allium* (*e.g.*, onion, leek, shallot, chives, Chinese chives) also contain large amounts of these so-called organosulfur compounds, which are responsible for the characteristic odor and flavor of alliums (3). Among the other chemical compounds found in alliums are glutathione, a cysteine-containing tripeptide, which is involved in anticarcinogenic action (4–6), and the potentially chemopreventive flavonols quercetin and kaempferol (7, 8). None of the studies reviewed in 1991 by Steinmetz and Potter (1) or reviewed in 1992 by Block *et al.* (9) specifically investigated the association between *Allium* vegetable consumption and lung cancer, although most evidence for a lower cancer risk associated with a higher intake of fruit and vegetables has been reported for lung cancer. All published studies on the association between *Allium* vegetable consumption and cancer used the case-control study design in which the exposure of interest is measured retrospectively. A large-scale prospective cohort study on diet and cancer was started in the Netherlands in 1986. In the Netherlands Cohort Study we assessed the usual consumption of onions and leeks, as well as the use of garlic supplements before cancer was diagnosed. Garlic supplements are reported to contain detectable amounts of potential chemopreventive garlic compounds (10) and are the most widely used dietary supplements among elderly persons in the Netherlands (11). In the present report we evaluate the association between onion and leek consumption, garlic supplement use, and the incidence of lung carcinoma after 3.3 years of follow-up.

MATERIALS AND METHODS

The Cohort. The prospective cohort study has been started in the Netherlands in 1986 among 58,279 men and 62,573 women ages 55–69 years, who completed a self-administered mailed questionnaire on habitual dietary intake, dietary supplement use, life-style characteristics, medical history, and other potential risk factors for cancer. The study population originated from 204 municipalities with computerized population registries. A description of the design of the study and the characteristics of the cohort has been published (12). Following the case-cohort approach for analysis of the study, a subcohort of 3500 subjects (1688 men and 1812 women) was randomly sampled from the large cohort and followed up for vital status. The entire cohort has been followed up for the incidence of cancer.

Follow-up for Cancer. The method of record linkage that has been developed to ascertain information on cancer incidence in the entire cohort has been published previously (13). In brief, personal identifying items have been linked with records of all nine cancer registries in the Netherlands and with PALGA, the Dutch network and National Database for Pathology. The computerized pathology reports provided by PALGA were coded according to ICD-O[3] (14) to make the information on topography and morphology analogous to the information provided by the cancer registries. The present analysis is restricted to cancer incidence in the first 3.3 years of follow-up (from baseline in September 1986 to December 1989). In this period completeness of follow-up is estimated to be 95% (15).

Population Available for Analysis. After excluding subjects from the entire case group who reported prevalent cancer other than skin cancer and subjects with incident *in situ* lung carcinoma, with lung cancer other than carcinoma (sarcoma, lymphoma, unspecified morphology), or without at least a microscopically confirmed diagnosis, 550 incident primary lung carcinoma cases (ICD-O codes T162.2–T162.9) were available for analysis. Information

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[3] The abbreviations used are: ICD-O, International Classification of Diseases for Oncology; COPD, chronic obstructive pulmonary disease; RR, rate ratio; CI, confidence interval.

on morphological characteristics was used to categorize these cases into four distinct histological subgroups: squamous cell carcinoma (ICD-O codes M8052–M8073); adenocarcinoma (M8140–M8560); small cell carcinoma (M8041–M8047); and large cell, other, and unspecified carcinoma (M8001–M8021) (14). From the subcohort, 3346 persons (1630 men and 1716 women) remained for analysis after excluding prevalent cancer cases other than skin cancer.

Questionnaire. A 150-item semiquantitative food frequency questionnaire was used to collect information on the usual intake of food and beverages in the year preceding the start of the study (16). Two of the questions on vegetable intake specifically focused on the consumption of *Allium* vegetables: "How many onions did you usually eat per week?"; and "How often have you consumed leeks in summer and how often in winter?." The latter question asked subjects, for each season, to choose from one of six categories ranging from "never or less than once per month" to "3–7 times per week," including leeks consumed in mixed vegetable dishes. Fresh garlic was not included as a separate food item in the questionnaire. The question on the use of dietary supplements was formulated as follows: "During the past 5 years did you use vitamin tablets, drops, or other preparations (*e.g.*, tonics, vitamins, garlic pills, brewer's yeast, calcium)?" In the open-ended part of this question information on type of dietary supplement, brand name, dose per day, as well as the specific period in which the consumption took place could be listed. The food and beverage part of the questionnaire has been validated against three 3-day diet records (16). The dietary supplement question has been validated as part of the larger validation study, using data from three interviews as a reference method (17).

Data Analysis. Questionnaire data of all cases and subcohort members have been key-entered twice and blinded with respect to case/subcohort status to avoid random and systematic coding errors. Subjects with incomplete or inconsistent dietary information were excluded from the analyses in which dietary variables were included (15). Thus, the analyses concerning onion and leek consumption are based on 484 lung carcinoma cases and 3123 subcohort members. Subjects were classified into four categories of onion consumption based on numbers per day: 0; ≤0.25; 0.25–0.5; and ≥0.5 onion/day. Classification of subjects according to leek consumption was based on the mean frequency of consumption in summer and winter: 0, ≤2; and >2 times/month. Garlic supplement users were defined as those respondents who reported the use of at least one garlic supplement per day for at least 1 year in the 5-year period preceding the baseline. Subjects with missing values on the dietary supplement question were excluded from the analysis, leaving 546 lung carcinoma cases and 3340 subcohort members available for analyses that did not include dietary variables.

Age, gender, smoking habits, highest educational level, history of COPD, lung cancer in first or second degree relatives, and vitamin C and β-carotene intakes from food were considered as potential confounders. Dietary vitamin C and β-carotene intakes were calculated using the computerized Dutch food composition table (18).

Case-cohort analyses were performed based on the assumption that survival times were exponentially distributed in this follow-up period (15). In stratified analyses we computed Mantel-Haenszel rate ratios and 95% confidence intervals for each of the onion and leek consumption categories adjusted for age, gender and smoking status, and tests for trend in the rate ratios. In the multivariable analyses, we also adjusted for other covariables. The 95% confidence intervals were corrected for the additional variance introduced by using a subcohort instead of the complete cohort. Tests for trend in the rate ratios were based on likelihood ratio tests. Analyses were conducted for all cases combined, for men and women separately, for all cases without those diagnosed in the first year after baseline. Analyses were also carried out for each of the four histological subtypes of carcinoma, since the association between vegetable intake and lung carcinoma risk may differ between histological types (19, 20).

The rate ratios and corrected 95% confidence intervals computed in stratified and multivariable analyses of the relation between garlic supplement use and lung carcinoma are reported in a separate table for all cases combined and in strata of smoking status. Since a large proportion of the garlic supplement users took other dietary supplements as well, the relation with lung carcinoma was also evaluated for those using exclusively garlic supplements with those not taking supplements as reference and for those using garlic together with any other supplement with those using any other supplement as reference.

RESULTS

A description of the 484 lung carcinoma cases and 3123 subcohort members with complete dietary data is presented in Table 1. Overall, there are large differences in the distribution of gender, age, smoking habits, and history of chronic obstructive pulmonary disease between cases and subcohort members. The differences in relative frequencies of highest educational level were less marked and those of lung cancer in close relatives very small.

Table 2 shows the distribution of onion and leek consumption in all 484 lung carcinoma cases and the four histological subgroups and in the 3123 subcohort members with complete dietary data.

Compared with the subcohort, onion consumption was lower and varied by histological subtype of the cases. Among squamous cell carcinoma, adenocarcinoma and small cell carcinoma cases the proportions in the highest onion consumption category were lower than among subcohort members, while among large cell and other carcinoma cases the proportion in this category was higher. The largest difference in proportion nonusers between cases and subcohort was seen for small cell carcinoma cases (31.5 and 20.7%, respectively). Comparison of the distribution of leek consumption in cases and subcohort members revealed a higher proportion of nonusers and a lower proportion in the "≤2 times/month" category in the case group. Except in small cell carcinoma cases, the proportions nonusers in the histological subgroups were higher than in the subcohort.

The distribution of garlic supplement consumption among cases and subcohort members is presented for the population of 546 cases and 3340 subcohort members with complete data on dietary supplement use. The proportion of persons consuming only garlic supplements (*i.e.*, without any other supplement) was slightly higher in all cases than in the subcohort, whereas the proportion of subjects who used garlic together with any other supplement was lower in the cases. Other dietary supplements used by the 19 lung carcinoma cases who reported the use of any other supplement together with garlic were brewer's yeast (26.3%), vitamin C (5.3%), vitamin B complex

Table 1 *Distribution of lung carcinoma cases and subcohort members with complete dietary data by various nondietary baseline characteristics*

Characteristics	n %	Subcohort
Total	484	3123
Gender		
Men	430 (88.8)	1525 (48.8)
Women	54 (11.2)	1598 (52.2)
Age (yr)		
55–59	124 (25.6)	1198 (38.4)
60–64	176 (36.4)	1082 (34.6)
65–69	184 (38.0)	843 (27.0)
Smoking habits[a]		
Never	14 (2.9)	1090 (34.9)
Ex-cigarette/only pipe-cigar	178 (36.8)	1157 (37.0)
Current cigarette smoker		
1–9/day	21 (4.3)	192 (6.1)
10–19/day	143 (29.5)	409 (13.1)
≥20/day	128 (26.4)	275 (8.8)
Highest educational level[a]		
Primary school	147 (30.8)	933 (30.1)
Lower vocational	125 (26.2)	683 (22.0)
Secondary/medium vocational	155 (32.4)	1080 (34.8)
University/higher vocational	51 (10.7)	406 (13.1)
History of COPD		
No	400 (82.6)	2842 (91.0)
Yes	84 (17.4)	281 (9.0)
Family history of lung cancer		
No	432 (89.3)	2810 (90.0)
Yes	52 (10.7)	313 (10.0)

[a] Numbers may not add up to 484 and 3123, respectively, due to missing values for some of the variables.

Table 2 *Proportions of onion and leek consumption and garlic supplement use among lung carcinoma cases with distinct histological characteristics and among subcohort members*

	Cases					
	Histological subtypes[a]					
Category of consumption	Sq	Ad	Sm	La	All	Subcohort
Onion consumption (no./day)						
0	20.5	20.0	31.5	18.8	22.1	20.7
≤0.25	33.3	35.2	25.8	30.0	31.8	29.5
0.25–0.5	36.7	36.2	29.2	35.0	34.9	35.2
≥0.5	9.5	8.6	13.5	16.3	11.2	14.7
Leek consumption (freq/month)						
0	37.1	36.2	28.1	41.3	36.0	30.6
≤2	32.4	36.2	40.4	27.5	33.9	38.8
>2	30.5	27.6	31.5	31.3	30.2	30.0
Garlic supplement use[b]						
No supplements	75.6	74.8	79.2	79.8	76.7	71.0
Exclusively garlic	6.0	4.5	5.2	4.5	5.3	4.6
Any other supplement	14.8	18.0	12.5	11.2	14.5	20.2
Garlic + any other supplement	3.6	2.7	3.1	4.5	3.5	4.2

[a] Sq, squamous cell carcinoma; Ad, adenocarcinoma; Sm, small cell carcinoma; La, large cell, other, and unspecified carcinoma.
[b] Proportions are presented for the total population available for analysis as described in "Materials and Methods." The categories of garlic supplement use are mutually exclusive.

(10.5%), and vitamin E (10.5%). The 140 subcohort members consumed vitamin C (24.3%), vitamin B complex (20.0%), vitamin AD (vitamin A with D combination) (9.3%), and vitamin E (7.9%) together with garlic supplements. In the category in which we grouped users of any other dietary supplement the following supplement types were reported by the 79 lung carcinoma cases and 675 subcohort members: vitamin C (27.8% and 25.3%); vitamin B complex (25.3 and 26.8%); vitamin AD (13.9% and 10.5%); and vitamin E (10.1 and 7.3%), respectively. The proportion of users of exclusively garlic supplements in the different histological subgroups was highest in squamous cell carcinoma cases (6.0%) and lowest in adenocarcinoma and large cell carcinoma cases (4.5%).

The proportions of subcohort members in the predefined categories of consumption of onions, leeks, and garlic supplements were examined across strata of other lung carcinoma risk factors (Table 3). Among the persons in the highest onion intake category were more men and less never smokers. In the highest leek consumption category were more women and more never smokers and less persons with a history of COPD. Among consumers of garlic supplements were more women, never smokers, persons with the highest level of education, history of COPD, and lung cancer in close relatives. In the highest onion and leek consumption category and among users of garlic supplements the mean vitamin C and β-carotene intakes were highest. The mean ages in the intake categories were almost similar.

Rate ratios and 95% confidence intervals for lung carcinoma according to categories of onion and leek consumption are presented in Table 4. In stratified analysis, in which we controlled for age, gender, and smoking status (never, ex-, current smoking), the consumption of at least 0.5 onion/day was negatively associated with lung carcinoma (RR_{MH} = 0.65; 95% CI 0.45–0.95). After further adjustment in multivariable analyses for highest level of education, history of COPD, family history of lung cancer, dietary intake of vitamin C and β-carotene, and pack years of past smokers and of current smokers (instead of smoking status), the RR for the highest category of onion consumption stayed below the null value (RR = 0.80) but was no longer significantly lower than 1 (95% CI 0.52–1.24). The other RRs suggested a positive association with onion consumption. None of the RRs for lung carcinoma associated with leek consumption were significantly different from unity. Neither of the trends in the rate ratios reached statistical significance.

The associations between onion and leek consumption and the risk of specific histological subtypes of lung carcinoma are also presented in Table 4. For squamous cell carcinoma and adenocarcinoma the associations with onion consumption were slightly higher than the null value, except in the highest intake category. Small cell carcinoma risk was negatively associated with onion consumption in stratified analysis, but the RRs increased slightly after further controlling for other risk factors in the multivariable analysis and were no longer significantly lower than 1. The association of onion consumption with large cell, other, and unspecified carcinoma varied among the intake categories. None of the trends in the rate ratios were statistically significant.

In stratified analyses, leek consumption was negatively associated with risk for squamous cell carcinoma, adenocarcinoma and large cell, and other carcinoma and positively associated with risk for small cell carcinoma, although not significantly. After adjustment for other risk factors, the RR for adenocarcinoma among those consuming leeks less or equal than 2 times/month was nearly significantly higher than one

Table 3 *Association between* Allium *vegetable consumption and garlic supplement use and potential lung carcinoma risk factors among subcohort members*

	Onion (no./day)				Leek (frequency/mo.)			Garlic supplement use	
Characteristics	0	<0.25	<0.5	≥0.5	0	≤2	>2	No[a]	Yes[b]
Proportion									
Men	48.5	51.3	45.3	52.9	50.9	50.2	45.0	53.4	40.4
Never smoking	40.1	33.9	35.0	29.4	34.3	34.1	36.5	33.7	39.0
University/high vocational education	13.1	13.7	12.5	13.3	11.1	15.4	12.1	10.9	11.5
History of COPD (yes)	8.0	7.5	10.5	9.8	9.0	10.1	7.5	8.5	9.2
Family history of lung cancer (yes)	7.3	10.0	11.4	10.7	8.9	9.8	11.4	10.4	11.3
Mean ± SD									
Age	61.7 ± 4.1	61.4 ± 4.3	61.2 ± 4.2	61.2 ± 4.0	61.7 ± 4.2	61.3 ± 4.3	61.2 ± 4.2	61.3 ± 4.2	61.8 ± 4.1
Vitamin C intake (mg/day)	93.4 ± 42.5	97.0 ± 39.1	107.8 ± 42.4	120.2 ± 47.2	96.4 ± 41.9	100.9 ± 39.6	113.7 ± 46.7	92.5 ± 47.2	112.6 ± 52.7
β-Carotene intake (mg eq vitamin A activity)	0.37 ± 0.23	0.37 ± 0.20	0.44 ± 0.25	0.51 ± 0.28	0.37 ± 0.22	0.39 ± 0.21	0.49 ± 0.27	0.30 ± 0.42	0.41 ± 0.42

[a] No supplements.
[b] Garlic with or without any other supplement.

Table 4 *Rate ratios and 95% confidence intervals of lung carcinoma according to Allium vegetable consumption, in stratified[a] and multivariable[b] analyses*

	Onion consumption (no./day)				Leek consumption (frequency/mo)		
	0	<0.25	0.25–0.5	≥0.5	0	≤2	>2
Person yr in subcohort	2071	2978	3554	1471	3096	3903	3092
All carcinoma							
No. of cases	107	154	169	54	174	164	146
RR_{MH} (95% CI)	1.00[c]	0.95 (0.71–1.28)	0.97 (0.76–1.29)	0.65 (0.45–0.95)	1.00[c]	0.79 (0.61–1.01)	0.96 (0.74–1.24)
RR (95% CI)	1.00[c]	1.91 (0.85–1.67)	1.25 (0.90–1.74)	0.80 (0.52–1.24)	1.00[c]	0.99 (0.75–1.30)	1.08 (0.80–1.45)
Trend test χ^2 (*P*)			0.15 (0.703)			0.29 (0.584)	
Squamous cell carcinoma							
No. of cases	43	70	77	20	78	68	64
RR_{MH} (95% CI)	1.00[c]	1.09 (0.72–1.65)	1.18 (0.79–1.78)	0.63 (0.36–1.11)	1.00[c]	0.78 (0.55–1.10)	0.97 (0.67–1.38)
RR (95% CI)	1.00[c]	1.51 (0.94–2.45)	1.66 (1.04–2.66)	0.86 (0.45–1.64)	1.00[c]	0.92 (0.63–1.35)	1.05 (0.70–1.59)
Trend test χ^2 (*P*)			0.16 (0.688)			0.04 (0.832)	
Adenocarcinoma							
No. of cases	21	37	38	9	38	38	29
RR_{MH} (95% CI)	1.00[c]	1.08 (0.62–1.85)	1.07 (0.62–1.83)	0.55 (0.26–1.17)	1.00[c]	0.89 (0.57–1.39)	0.86 (0.53–1.41)
RR (95% CI)	1.00[c]	1.03 (0.58–1.85)	1.08 (0.61–1.91)	0.57 (0.24–1.32)	1.00[c]	1.20 (0.99–1.97)	1.06 (0.61–1.87)
Trend test χ^2 (*P*)			0.77 (0.381)			0.07 (0.784)	
Small cell carcinoma							
No. of cases	28	23	26	12	25	36	28
RR_{MH} (95% CI)	1.00[c]	0.50 (0.28–0.88)	0.61 (0.36–1.04)	0.48 (0.24–0.97)	1.00[c]	1.27 (0.76–2.10)	1.30 (0.76–2.24)
RR (95% CI)	1.00[c]	0.67 (0.35–1.26)	0.87 (0.48–1.58)	0.59 (0.27–1.32)	1.00[c]	1.64 (0.93–2.91)	1.63 (0.89–2.97)
Trend test χ^2 (*P*)			1.05 (0.305)			2.83 (0.092)	
Large cell, other, and unspecified carcinoma							
No. of cases	15	24	28	13	33	22	25
RR_{MH} (95% CI)	1.00[c]	0.87 (0.47–1.64)	1.07 (0.59–1.96)	1.05 (0.51–2.15)	1.00[c]	0.61 (0.36–1.04)	0.89 (0.53–1.50)
RR (95% CI)	1.00[c]	0.95 (0.49–1.84)	1.26 (0.67–2.37)	1.20 (0.55–2.58)	1.00[c]	0.73 (0.42–1.26)	0.99 (0.57–1.74)
Trend test χ^2 (*P*)			0.69 (0.408)			0.01 (0.896)	

[a] RR_{MH} stratified by gender, age in three categories (55–59, 60–64, 65–69 years), and smoking status (never, ex-, and current smoker).
[b] RR adjusted for gender, age [continuous (c)], pack years of past-smokers (c), pack years of current smokers (c), highest level of education, history of COPD, family history of lung cancer, dietary intake of vitamin C (c) and β-carotene (c).
[c] Reference category.

(RR = 1.20; 95% CI 0.99–1.97). None of the tests for trend in the RRs were statistically significant.

Exclusion of the lung carcinoma cases diagnosed in the first year after baseline did not alter the rate ratio estimates (results not shown). In analyses for men and women separately, none of the rate ratio estimates were significantly different from unity (results not shown).

The association between garlic supplement use with lung carcinoma is presented in Table 5. Garlic supplement use was positively but not significantly associated with lung cancer after adjustment for age, gender, and smoking status in stratified analysis. The relationship with lung carcinoma was evaluated for those using exclusively garlic supplements with those not taking supplements as reference and for those using garlic together with any other supplement with those using

Table 5 *Rate ratios and 95% confidence intervals of lung carcinoma according to garlic supplement use in stratified and multivariable analyses*

	Garlic *vs.* no supplements			Garlic *vs.* any other supplement	
	No	Garlic supplements	Exclusively garlic supplements	Any other	Garlic + any other
Stratified analysis[a]					
Person yr in subcohort	7671	939	489	2180	450
No. of cases	419	48	29	79	19
RR_{MH} (95% CI)	1.00[b]	1.13 (0.79–1.62)	1.29 (0.80–2.08)	1.00[b]	0.85 (0.44–1.62)
Multivariable analysis[c]					
Person yr in subcohort	7122	899	460	2069	440
All cases	323	36	23	65	13
RR (95% CI)	1.00[b]	1.22 (0.81–1.86)	1.78 (1.08–2.92)	1.00[b]	0.93 (0.46–1.86)
Never smokers[d]					
Person yr in subcohort	2376	345	187	825	158
No. of cases	14	5	4	1	1
RR (95% CI)	1.00[b]	2.42 (0.83–7.11)	3.27 (0.99–10.77)		
Ex smokers[e]					
Person yr in subcohort	2702	329	150	707	179
No. of cases	124	14	9	34	5
RR (95% CI)	1.00[b]	1.03 (0.32–1.92)	1.37 (0.62–2.99)	1.00[b]	0.53 (0.18–1.58)
Current smokers[f]					
Person yr in subcohort	2044	226	123	537	103
No. of cases	219	20	11	34	9
RR (95% CI)	1.00[b]	1.02 (0.57–1.83)	1.47 (0.70–3.08)	1.00[b]	1.34 (0.55–3.28)

[a] Stratified by gender, age (55–59, 60–64, 65–69 years), and smoking status (never, ex-, current).
[b] Reference category.
[c] Adjusted for gender, age [continuous (c)], pack years of past smoking (c), pack years of current smoking (c), highest educational level, history of COPD, onion and leek consumption, and dietary intake of vitamin C (c) and β-carotene (c).
[d] Adjusted for gender, age (c), highest educational level (low-medium-high), history of COPD.
[e] Adjusted for gender, age (c), pack years of past smoking (c), highest educational level, history of COPD.
[f] Adjusted for gender, age (c), pack years of current smoking (c), highest educational level (low-medium-high), history of COPD.

any other supplement as reference. The RR_{MH} for those subjects using exclusively garlic supplements was higher than for subjects using garlic supplements with or without any other supplements [1.29 (95% CI 0.80–2.08) and 1.13 (95% CI 0.79–1.62, respectively]. The RR_{MH} for those using garlic with any other supplement was lower than for those in the reference category who consumed any other supplement (0.85, 95% CI 0.44–1.62). In the multivariable analysis we show the results of two models. The first model included all covariables also used in the analyses of onion and leek consumption. Compared to those not using supplements, the RR for those using garlic supplements with or without any other supplement was not significantly higher than the null value. The positive association observed for exclusively garlic, however, was statistically significantly (RR = 1.78; 95% CI 1.08–2.92). Lung carcinoma was negatively associated with garlic together with any other supplement use, compared to any other supplement use (RR = 0.93; 95% CI 0.46–1.86). Exclusion of cases diagnosed in the first year after baseline did not alter these results (data not shown). In the analyses in strata of smoking status, we adjusted for fewer covariables than in the first model and categorized highest educational level in three categories (low-medium-high). Among the never smokers a higher RR was observed for those using exclusively garlic supplements (RR = 3.27; 95% CI 0.99–10.77) compared with the RRs among ex- or current smokers (RR = 1.37; 95% CI 0.62–2.99, and RR = 1.47; 95% CI 0.70–3.08, respectively). Associations with garlic together with any other supplement use could be evaluated only within strata of exsmokers and current smokers. Among exsmokers the RR for lung carcinoma was lower than among current smokers (RR = 0.53; 95% CI 0.18–1.58 and RR = 1.34; 95% CI 0.55–3.28, respectively). None of the associations with garlic supplement use within strata of smoking status were significant.

DISCUSSION

In the Netherlands Cohort Study we found no evidence of an association between onion and leek consumption and the risk of lung carcinoma or any of its histological subtypes after adjustment for confounders. The observed rate ratio estimates associated with garlic supplement use were inconsistent.

Evaluation of the risk of cancer associated with *Allium* consumption is important since the consumption of *Allium* vegetables has been suggested to have a negative effect on the risk of several cancer sites (1, 9). The relation with lung cancer has not been studied yet, although most evidence for a lower cancer risk associated with vegetable intake has been reported for lung cancer (1, 9), and lung cancer is an important cause of cancer morbidity and mortality. In the Dutch population lung cancer was the most frequent tumor in males and the fourth most common cancer in females in 1989 (21). In two earlier studies on the association between consumption of vegetables and risk of lung cancer *Allium* vegetable intake was assessed, but in neither study was the risk of lung cancer specifically evaluated for *Allium* vegetable consumption. A recently published report from the Iowa Women's Health Study, a prospective cohort study, showed a significantly lower lung cancer risk for high intake of all vegetables including leeks, scallions, and fresh garlic; the age-, smoking-, and energy-adjusted odds ratio was 0.50 (95% CI 0.29–0.87) (22). In 1992, a case-control study from China was published on the risk of lung cancer associated with fresh green vegetables (Chinese chives, strip onions, and fragrant flowered garlic as well as Chinese cabbage, green chilli, mint, and bean sprouts). A lower lung cancer risk was observed for the more frequent consumers of fresh green vegetables after adjustment for age group, respondent type, study site, education, and income (odds ratio, 0.24) and within strata of smoking status (23).

Absence of an association between *Allium* vegetable consumption and lung carcinoma risk may be explained by factors associated with the design and conduct of the study, as well as with the proposed mechanism of action of the potential anticarcinogenic compounds in alliums.

Selection bias due to loss of follow-up is unlikely since the completeness of follow-up of vital status in the subcohort was 100% and that of cancer incidence was 95% (15). By including many other, nondietary as well as dietary, known determinants of lung carcinoma in the multivariable models, we thoroughly controlled for potential confounding: the RR of 0.65 (95% CI 0.45–0.95) observed in the stratified analysis for users of at least 0.5 onions/day increased to 0.80 (95% CI 0.52–1.21) in the multivariable analysis by including pack years for past and current smokers as continuous variables in the model, instead of using smoking status categorized as never, ex-, or current smoking. The RR stayed below the null value after controlling for the other potential risk factors but was not significantly different from unity. Another explanation for absence of an association might be that the follow-up period is still relatively short (3.3 years). Preclinical symptoms of disease might have influenced the intake of *Allium* vegetables. Exclusion of cases diagnosed in the first year of follow-up, however, did not change the results. It is uncertain whether the absence of a relation between *Allium* vegetable consumption and lung carcinoma risk might have been caused by misclassification of exposure, since the validity of the semiquantitative food frequency questionnaire has not been assessed for the questions on onion and leek consumption specifically (16). Unfortunately, we were not able to evaluate if fresh garlic use was associated with the risk of lung carcinoma, since a separate question on fresh garlic consumption was not included in the semiquantitative food frequency questionnaire administered in 1986. However, in a questionnaire that was completed by members of the subcohort 4 years after the baseline, 71% of the respondents reported that they never used fresh garlic, 12.5% used up to 1 garlic clove/week, and only 1.6% consumed at least 1 clove/day.

The elevated risk for lung carcinoma associated with daily consumption of garlic supplements was unexpected, since garlic supplements are claimed to contain detectable amounts of antimutagenic or even anticarcinogenic garlic compounds (10). The relative risk of lung carcinoma was notably higher in the never smoking stratum then in the other smoking strata, although not significantly. However, since the number of cases was not very high, we had to define broader categories of education and exclude other determinants from the analyses per smoking stratum. Misclassification of exposure is a less plausible explanation for the higher risk, since recall of intake of garlic supplements was 77.8%, which may provide enough precision to correctly classify individuals into distinctive categories of intake (17). Excluding cases from the first year after baseline did not change the results, suggesting no influence of preclinical disease on the consumption of garlic supplements. Garlic supplement use in combination with any other supplement compared with the use of any other supplement as reference was associated with a lower risk for lung carcinoma in nonsmokers and exsmokers, while for those using exclusively garlic supplements a higher risk was observed in these strata. This discrepancy cannot be explained simply by differences in distribution of the other dietary supplement types, since cases and subcohort members consumed roughly the same types of other supplements. Although we cannot easily explain the observed risk of lung carcinoma for garlic supplement use, it can be concluded that garlic supplements are not associated with a lower risk of lung carcinoma.

Other possible explanations for the absence of a relationship between onion and leek consumption and lung carcinoma incidence are related to the biological activity of the potential chemopreventive compounds. Quercetin, the principal flavonol present in onions, might act as anticarcinogen (24), although quercetin and related flavonols are also reported to be mutagenic (6, 25). Kaempferol, predominantly present in leeks (26), inhibits aflatoxin B_1-induced mutagenesis (27) but might also act as anticarcinogen (7). The level of flavonols in onions and leeks, however, varies by variety, season, storage conditions, method of preparation, and by part of the plant (28–32). For instance, the outer dark green leaves of leek have a higher kaempferol content than the inner leaves (32), and the dry skins of onions have a higher quercetin content than the inner rings. In some onion varieties, quercetin is not even detectable in the inner rings (26). In garlic only traces of flavonols have been found (29). Glutathione, another compound present in *Allium* vegetables, is also reported to be anticarcinogenic (4, 5). Both flavonols and glutathione are widely distributed in foods (5, 29). Onions are the second most important contributors of quercetin intake in adults in the Netherlands (33). However, the ingested amount of potential chemopreventive compounds contributed by eating *Allium* vegetables might not be high enough to have a detectable effect on the risk of lung carcinoma in humans.

Organosulfur compounds are predominantly present in *Allium* vegetables and account for their typical odor and flavor (3, 34). The principal groups of organosulfur compounds are the propyl-, methyl-, and allyl-containing compounds, formed when the vegetables are cut. Onions and leeks have large proportions of propyl derivatives, while garlic has mainly allyl-containing compounds (35). However, the quantity of organosulfur compounds also depends on temperature, storage conditions, soil conditions, climate, chemical treatment, and variety (36, 37).

To exert its potential chemopreventive action on lung cancer a potential anticarcinogen must be absorbed after consumption. A study in four volunteers showed that less than 1% of quercetin when given in high doses (4 times the estimated daily intake) did reach the general circulation (38). The uptake of glutathione, which is normally present in interalveolar cells in the lung (not in alveolar cells) (4), has to our knowledge been evaluated only in animals (39). Specific data on the bioavailability of organosulfur compounds from onions, leeks, and garlic supplements are also not available for humans. The possibility that the potential chemopreventive compounds in alliums act only or predominantly in a very early stage in carcinogenesis or against specific chemical carcinogens (7, 40) might also explain the absence of a lower risk associated with onion and leek consumption, since its action must then prevent initiation-related activities, which occur quickly and take place at a specific time and place in the presence of specific carcinogens (41, 42). For flavonols and garlic compounds both anti-initiating and antipromoting activity has been demonstrated (2, 24).

In conclusion, we found no evidence of a relation between the consumption of onions or leeks and the risk of lung carcinoma or any histological subtype of lung carcinoma. Although the increased rate ratio estimates for garlic supplement use cannot easily be interpreted, we conclude that garlic supplements are not associated with a lower risk of lung carcinoma.

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